

REMARKS

I. Status Summary

Claims 1-27, 46-53, and 60-75 are pending and have been examined. Applicants respectfully note that the Official Action dated September 21, 2006 (hereinafter "the Official Action") states in the Official Action Summary that claims 1-27, 46-53, and 61-75 are pending. Applicants respectfully submit that this appears to be a typographical error.

Claims 1-27, 46-53, and 60-75 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not enable the full scope of the claims.

Claims 1-27, 46-53, and 60-75 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that there are certain phrases in the claims that are indefinite.

Claims 1-10, 60, and 75 have been rejected under 35 U.S.C. § 102(a) upon the contention that the claims are anticipated by Howard *et al.* (2000) 11 *Mammalian Genome* 234-237 (hereinafter "Howard").

Claims 1-10, 15, 19-27, 46-53, 64-73, and 75 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) *Proc Natl Acad Sci USA* 94:5231-5236 (hereinafter "Diehl").

Claims 11-14, 16-18, and 63-74 remain rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) *J. Immunol* 137:2355-2360 (hereinafter "Dindzans"), and further in view of Hedrich (1981) Genetic Monitoring, Volume 1, Chapter 8 (hereinafter "Hedrich"). Claims 1-10, 15, 19-27, 46-53, and 60-75 also remain rejected under this section over the combination of Lipp *et al.* (1999) *J APOA Intl* 82:923-928 (hereinafter "Lipp") in view of U.S. Patent No. 6,573,438 to Mettler et al. (hereinafter "the '438 Patent").

Claim 75 has been canceled without prejudice. Applicants hereby reserve the right to file one or more continuing patent applications with claims directed to the subject matter of canceled claim 75.

Claims 1, 2, 46, 47, 60, 64, and 74 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly in

Figure 1 and in the Brief Description of Figure 1 at page 8, lines 19-27 (regeneration of genomes; intercrossing recombinant individuals for one generation). Additional support can be found at page 6, lines 14-19 (intercrossing or backcrossing recombinant inbred individuals). Accordingly, no new matter has been added as a result of the claim amendments.

New claims 76 and 77 have been added. Support for the new claims can be found throughout the specification as filed, including particularly at page 6, lines 18-20. Accordingly, no new matter has been added as a result of the addition of the new claims.

Reconsideration of the application based on the amendments and remarks set forth below is respectfully requested.

II. Summary of the March 1, 2007 Telephone Interview

On March 1, 2007, a telephone interview was held between applicants' representatives Arles A. Taylor, Jr. and Christopher P. Perkins and Examiners Johannsen and Shaw of the United States Patent and Trademark Office (hereinafter "the Patent Office").

The telephone interview began with a summary by applicants' representatives of the presently claimed subject matter. Summarily, applicants' representatives indicated that the presently claimed subject matter related generally to genetic mapping methods in which the population of individuals that were mapped represented at least one point of novelty of the presently claimed subject matter over what was understood to be disclosed in the cited art with respect to genetic mapping.

More particularly, applicants' representatives described the presently claimed subject matter as a mapping method wherein a renewable population of genetically diverse individuals is generated and the genomes of this renewable population are mapped in order to identify genetic loci that modulate phenotypes of interest. This led to a discussion about certain aspects of the claim language, particularly what was intended by the phrases "genetically diverse" and "renewable population". With respect to the former, it was explained that a "genetically diverse" individual was an individual that was heterozygous for at least one detectable polymorphism. Thus, "genetically

diverse” refers to an individual that is not homozygous at every locus (*i.e.*, has different alleles at one or more loci). It was pointed out that members of recombinant inbred strains are not genetically diverse because each individual has been bred to be homozygous at every locus (hence the term “inbred”).

With respect to “renewable population”, this was described as a population that can be faithfully regenerated. More particularly, it was stated that what must be faithfully regenerated in order to render a population “renewable” are the genomes of the individuals in the population. Thus, natural human populations are not renewable because, for example, if person A and person B were to have a child C, they would not be able to subsequently conceive any other child that was genetically identical to child C because meiotic recombination randomizes the assortment of genes passed on from each parent to each progeny individual. Simply stated, matings of natural populations (*i.e.*, not inbred populations) cannot produce renewable populations.

In light of this framework, the currently pending rejections were discussed generally. Particularly, Examiners Johannsen and Shaw indicated that if the claim language was presented in a manner consistent with the discussion, it would be possible and even likely that the rejections under 35 U.S.C. § 112, first and second paragraphs, would be withdrawn. Additionally, Examiners Johannsen and Shaw indicated that the rejection under 35 U.S.C. § 112, second paragraph, over the phrase “less than about” was likely to be withdrawn based on closer consideration of the factual background of the *Amgen v. Chugai* case.

Turning now to the rejections under 35 U.S.C. §§ 102 and 103, Examiners Johannsen and Shaw indicated that if the claim language was presented in a manner consistent with the issues discussed in the telephone interview, a new search would probably be required.

Applicants would like to thank Examiners Johannsen and Shaw for their time and efforts in discussing the instant subject matter during the March 1, 2007 telephone interview. Applicants respectfully submit that the amendments and remarks presented herein are believed to be consistent with the discussions of the telephone interview.

III. Response to the Enablement Rejection

Claims 1-27, 46-53, and 60-75 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification does not enable the full scope of the claims. Although the Patent Office asserts that the specification enables a method comprising (a) providing a renewable population of genetically diverse mice that can be regenerated wherein a plurality of the genetically diverse mice are heterozygous to a detectable polymorphism; (b) mapping the genomes of mice within the renewable population of genetically diverse mice that display a particular body weight; and (c) identifying a genetic locus on chromosomes 4, 6, and 12 that modulates the body weight through the mapping of step (b), the Patent Office asserts that the specification as filed does not enable a method for identifying any locus that modulates any phenotype in any organism.

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and present the following remarks.

Initially, applicants respectfully submit that during the telephone interview dated March 1, 2007, Examiners Johannsen and Shaw indicated that the instant rejection was likely to be withdrawn. As such, applicants submit the following remarks in an abundance of caution with this understanding in mind.

Applicants respectfully submit that the Patent Office has not established a *prima facie* case of lack of enablement of the instant claims. Particularly, applicants respectfully submit that the discussion of the *Wands* Factors presented in the Official Action is incomplete and does not fully take into account those considerations that support the enablement of the claims.

For example, the Patent Office appears to assert with respect to the "Nature of the Invention" Factor that the CAFC has held that any discipline that falls within the fields of chemistry or biology is highly unpredictable. Applicants respectfully submit that the *Mycogen Plant Sci.* case cited does not stand for this proposition. In fact, the quoted phrase appears in the *Mycogen Plant Sci.* case in relation to the doctrine of simultaneous conception and reduction to practice, not enablement. The art of genetic mapping to which the presently disclosed subject matter relates, however, is a mature field that is generally not considered so unpredictable that one of ordinary skill in the art

would not have generally have a reasonable expectation of being able to map genetic loci provided that proper mapping populations and genomic landmarks (e.g., markers for which the genomic location is known) are available. Therefore, applicants respectfully submit that the Patent Office has applied a very broad generalized statement by the CAFC without consideration of whether this specific technique would in fact be considered unpredictable by one of ordinary skill in the art.

Furthermore, with respect to the "Teachings in the Specification and State of the Art" Factor, the Patent Office appears to recognize that practice of the presently disclosed methods resulted in the identification of additional genetic loci that were associated with two representative quantitative traits compared to the then state of the art recombinant inbred (RI) mapping technique. However, the Patent Office then appears to imply that the success of the methods for mapping loci that modulate these representative quantitative traits is not indicative of the applicability of the methods to map other genetic loci or in other species. Applicants respectfully submit that these quantitative traits are intended to be representative of quantitative traits generally, and one of ordinary skill in the art would understand that the presently disclosed methods are applicable to genetic mapping of any phenotype.

It is respectfully submitted that the application of the claimed methods to mapping in mice, for example, would be understood by one of ordinary skill in the art to demonstrate that the methods could also be successfully employed on other animals or even plants. Applicants respectfully submit that the success of the method depends not on the species and/or the quantitative trait chosen and thus one of ordinary skill in the art would understand after consideration of the instant disclosure that the technique would indeed be applicable to non-murine individuals and populations.

Continuing with the instant rejection, the Official Action next discussed the "Predictability or Unpredictability of the Art and the Degree of Experimentation" Factor. The Patent Office asserts that the art of identifying a genetic locus that modulates a phenotype is "highly unpredictable". This position is respectfully traversed. Even the Belknap reference cited by the Patent Office indicates that even if individual mapping experiments can be prone to error, that this error "is not insurmountable".

Thus, even if “error” could be equated with “unpredictability”, which applicants respectfully submit is not the case, Belknap suggests that those of ordinary skill in the art had an appreciation for the impact error might have on a mapping experiment and have found strategies to minimize and/or overcome it. Applicants respectfully submit that the import of this disclosure is that the unpredictability is believed to be considerably less than the Patent Office appears to assert in the instant Official Action.

Additionally, applicants respectfully submit that proper consideration of this Factor does not require that the genetic loci identified as modulating body weight on mouse chromosomes 4, 6, and 12 or that modulate brain weight on mouse chromosomes 5 and 11 be extrapolated to other organisms. Applicants respectfully submit that it is not required for a successful genetic mapping experiment that a locus identified in one species have an ortholog in another species on the same chromosome or indeed that the other species have an ortholog of the identified locus at all. It may be the case that there are orthologs in other species, particularly closely related species evolutionarily, and it even may be that the orthologs are found in regions that are syntenic between the species. Applicants respectfully submit that this is not required in genetic mapping, however.

Continuing, with respect to the “Amount of Direction” Factor, the Patent Office appears to suggest that use of Map Manager QTX “may involve extensive experimentation”, and further that this experimentation is “random, trial by error experimentation” that is “highly unpredictable”. Applicants respectfully submit that one of ordinary skill in the art would not expect genetic mapping to be characterized by random or trial and error experimentation.

Additionally, concerning the “Working Examples” Factor, it is believed that the specific working examples disclosed would lead one of ordinary skill in the art to understand that the methods claimed are much more broadly applicable than just these traits. Also, one of ordinary skill in the art would understand that the methods are not limited only to genetic mapping in mice, and further that the methods are applicable to phenotypes that result from an interaction between genetic and non-genetic factors.

Accordingly, applicants respectfully submit that a *prima facie* case of lack of enablement of claims 1-27, 46-53, and 60-75 has not been presented. Claim 75 has

been canceled, and thus the instant rejection is believed to be moot as to this claim. As such, applicants respectfully request that the instant rejection of claims 1-27, 46-53, and 60-74 be withdrawn, and that the claims be allowed at this time.

IV. Response to the § 112, Second Paragraph Rejection

Claims 1-27, 46-53, and 60-75 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that certain phrases recited in the claims are indefinite. Particularly, the Patent Office has asserted that (a) the phrase "a population of genetically diverse individuals" is considered unclear because the phrase "is not clearly defined in the specification and there is no art recognized definition for this phrase"; and (b) the phrases "less than about 500" and "less than about 100" are unclear under the holding of *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (CAFC 1991).

Applicants respectfully disagree. Initially, applicants respectfully submit that 35 U.S.C. § 112, second paragraph does not require that each term or phrase recited in a claim be characterized by an art recognized definition or a "clear" definition present in the specification. Rather, applicants respectfully submit that 35 U.S.C. § 112, second paragraph only requires that a claim term or phrase be sufficiently clear so that one of ordinary skill in the art would understand the metes and bounds of the claim terms after review of the specification. Applicants respectfully submit that this requirement is believed to be met in the present claims.

To elaborate, applicants respectfully submit that the phrase "a population of genetically diverse individuals" refers to a population of individuals that are genetically diverse. With respect to "genetically diverse", this phrase (and grammatical variants thereof) is intended to indicate that the individuals are not genetically homogeneous. Stated another way and with respect to an individual genome, "genetic diversity" refers to heterozygosity. Therefore, a genetically diverse individual is an individual that is not homozygous at every locus (e.g., is not inbred).

Applicants respectfully submit that this meaning is supported by the specification when considered as a whole. Particularly, the specification discloses that methods that can be employed to generate a population of genetically diverse include, but are not

limited to intercrossing recombinant inbred (RI) lines and backcrossing RI lines. Given that one of ordinary skill in the art knows that individuals of an RI line are homozygous at every locus, upon a review of the instant disclosure one of ordinary skill in the art would also understand that what crossing these lines would accomplish would be to reproducibly introduce heterozygosity in the genomes of the progeny.

Accordingly, applicants respectfully submit that one of ordinary skill in the art would understand what is intended by the phrase "a population of genetically diverse individuals" based on a consideration of the specification as a whole. Thus, applicants respectfully request the instant rejection of the claims under 35 U.S.C. § 112, second paragraph, be withdrawn at this time.

Turning now to the second basis for the instant rejection, applicants respectfully submit that Examiners Johannsen and Shaw indicated during the March 1, 2007 telephone interview that the rejection under 35 U.S.C. § 112, second paragraph, over the phrase "less than about" was likely to be withdrawn based on closer consideration of the factual background of the *Amgen v. Chugai* case. Particularly, Examiners Johannsen and Shaw indicated that the specific facts considered by the Court of Appeals for the Federal Circuit (CAFC) in the *Amgen* case are not present with respect to the instant claims, and thus the holding of this case is not applicable to the instant claims.

To elaborate, applicants respectfully submit that the CAFC held that the phrase "less than about" was indefinite where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about". See *also* M.P.E.P. § 2173.05(b). Applicants respectfully submit that this situation is not confronted with respect to the instant claims, and thus applicants respectfully submit that *Amgen's* holding is not applicable.

Therefore, applicants respectfully request that the instant rejection under 35 U.S.C. § 112, second paragraph, be withdrawn. Claim 75 has been canceled, and thus the instant rejection is believed to be moot as to this claim. Accordingly, applicants respectfully request that the instant rejection of claims 1-27, 46-53, and 60-74 be withdrawn at this time.

V. Responses to the Anticipation Rejections

Claims 1-10, 60, and 75 have been rejected under 35 U.S.C. § 102(a) upon the contention that the claims are anticipated by Howard *et al.* (2000) 11 *Mammalian Genome* 234-237 (hereinafter "Howard"). Claims 1-10, 15, 19-27, 46-53, 64-73, and 75 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) *Proc Natl Acad Sci USA* 94:5231-5236 (hereinafter "Diehl").

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and present the following remarks.

V.A. The Rejection Over Howard

According to the Patent Office, Howard teaches a method comprising (a) providing a renewable population of genetically diverse individuals; and (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified. Specifically, the Patent Office asserts that Howard teaches that the recombinant inbred lines AXB and BXA (which are both homozygous) were both used to study a mouse mutation that causes altered mammary gland development. Backcross and intercross of the AXB and the BXA lines display both alterations in the number and placement of nipples. Approximately 25% of both the AXB and BXA intercrosses and approximately 50% of the female backcross mice observed the mutant phenotype. Howard is also asserted to teach that they are now mapping the *ska* gene in the AXB/BXA recombinant inbred strains of mice and in the back cross and intercross panels in order to make a high resolution map to isolate the *ska* locus.

Applicants respectfully submit that a close reading of Howard does not support the Patent Office's assertions. First, applicants respectfully submit that Howard does not teach providing a renewable population of genetically diverse individuals that are heterozygous for a detectable polymorphism as recited in the instant claims.

To elaborate, Howard discloses on page 235 that "[c]rosses of AXB and BXA resulted in a total of 115 F₁ progeny" and that these mice were then backcrossed and intercrossed. However, it should be noted that while the nomenclature "AXB" and "BXA" frequently refer to RI lines established from A/J and C57BL/6 mice, in the instant

reference the nomenclature is being used to specify individual breedings of A/J and C57BL/6 mice to produce F₁ progeny and not the establishment of RI lines from these F₁ progeny. Essentially, the authors have employed "AXB" to refer to breeding a female A/J mouse to a male C57BL/6 mouse, and "BXA" to refer to the reciprocal breeding pair (*i.e.*, a male A/J mouse to a female C57BL/6 mouse). This is shown in Table 1. Since A/J and C57BL/6 mice are inbred mice, however, the 115 F₁ mice produced would be genetically identical, and thus these mice would not be employed as a mapping population.

Howard then discloses intercrosses and backcrosses, but these crosses are intercrosses and backcrosses of the F₁ animals as shown in Table 2 of Howard. An intercross or a backcross of an F₁ mouse would result in an F₂ generation that was not genetically identical, and could thus be employed in a mapping technique. However, the population of F₂ mice produced would not be renewable because the genomes in the F₂ generation could not be regenerated. The occurrence of meiotic recombination in the F₁ parents would rearrange the assortment of genetic materials in the parental gametes in a way that is not reproducible from gamete to gamete or generation to generation. Therefore, applicants respectfully submit that even if Howard were generating the backcross and/or intercross mice in order to perform genetic mapping on them, since these mice are not "renewable" as that term is employed in the instant claims, Howard cannot be read to anticipate the instant claims.

Additionally, the only populations that appear to be employed in a genetic mapping strategy are the AXB/BXA RI lines. However, as disclosed in the instant specification, RI lines are not genetically diverse, and thus mapping using RI lines is not mapping the genomes of individuals within the renewable population of genetically diverse individuals as recited in the instant claims.

Accordingly, applicants respectfully submit that Howard does not support the instant rejection of claims 1-10, 60, and 75. Claim 75 has been canceled, and thus the instant rejection is believed to be moot as to this claim. Accordingly, applicants respectfully request that the instant rejection of claims 1-10 and 60 be withdrawn at this time.

V.B. The Rejection Over Diehl

Turning now to the rejection over Diehl, the Patent Office asserts that Diehl teaches a method for identifying multiple genetic loci that modulate facial clefting in mice. Applicants respectfully submit, however, that Diehl does not support a rejection under of the claims under 35 U.S.C. § 102(b) because Diehl does not teach each and every element of the claims.

Initially, applicants respectfully submit that the Patent Office has presented certain assertions in support of the instant rejection that are inaccurate. First, the Patent Office asserts that the RI mice supplied by M. Nesbitt were “bred by intercrossing recombinant inbred lines and maintained in a colony at the University of Michigan as a renewable population of genetically diverse individuals” (see Official Action at page 12). Applicants respectfully disagree. Applicants respectfully submit that Diehl states that the RI lines were “bred and maintained in a colony at the University of Michigan” (see page 5232 of Diehl). There is no disclosure that the RI lines were intercrossed, as one of ordinary skill in the art would understand that intercrossing RI lines would destroy the RI lines. Rather, the breedings that maintain RI lines would be construed and understood by one of ordinary skill in the art to be sib matings (*i.e.*, matings of brother and sister of the same line). This is the only way to maintain an RI line, and it is believed to be what was done by the co-authors of Diehl.

In response to arguments previously submitted by applicants, the Patent Office contends that Diehl teaches that “A/J (heterozygous) was crossed with C57BL6/J (heterozygous) to produce the recombinant inbred lines AXB and BXA (which are both homozygous)”. Applicants respectfully submit, however, that this assertion represents a misunderstanding of the process that is used to create RI lines. Applicants respectfully submit that the nomenclature “AXB” and “BXA” here refers to RI lines that were established using the A/J and C57BL6/J non-recombinant inbred lines, each of which is homozygous at every locus. More specifically, the A/J line is not a line created by crossing the A mouse strain with the J mouse strain. Rather, “A/J” refers to the version of the “A” mouse strain that is sold by the Jackson Laboratory of Bar Harbor, Maine. Similarly, the nomenclature “C57BL6/J” refers to the version of the C57BL/6 mouse strain that is sold by Jackson Labs. See *also* Diehl at page 5232, which references the

A strain and the B strain, particularly the Jackson Labs versions, in the first paragraph of the Materials and Methods. Thus, the Patent Office's assertion that A/J mice are heterozygous or that C57BL6/J mice are heterozygous is incorrect. These mice are members of non-recombinant inbred strains and are thus homozygous at every locus. Thus, applicants respectfully submit that Diehl does not disclose intercrossing of RI lines.

Second, the Patent Office asserts that to map the genetic loci responsible for clefting, "the AXB and the BXA lines would have been crossed and their progeny would produce heterozygotes", which appears to be a response to applicants' assertion that Diehl does not disclose any breeding strategy that produces genetically diverse individuals. The Patent Office contends that since the individuals produced by crossing AXB and BXA are heterozygotes, they are technically genetically diverse with respect to each other.

Applicants respectfully disagree. Applicants respectfully submit that the Patent Office is misinterpreting how RI lines are generated and employed in mapping techniques. Applicants respectfully direct the Patent Office's attention to **Exhibits A** and **B** submitted with Amendment D dated December 5, 2003, true and accurate magnified black-and-white copies of which are re-submitted herewith. As shown in these **Exhibits** and as known to one of ordinary skill in the art, RI lines are typically generated by an initial breeding of two non-recombinant inbred lines (e.g., A/J (A), C57BL/6 (B), C3H (C), and DBA (D) in the **Exhibits**) to produce an F1 generation, the members of which are genetically identical to each other. Members of the F1 generation are bred to each other to produce an F2 generation, the members of which are genetically different from each other due to recombination events that take place in the F1 generation. Members of the F2 generation are then bred to each other to form an F3, and the members of the F3 are inbred by at least 20 generations of brother-sister matings (referred to as "sib matings") to produce recombinant inbred lines. Different pairs selected in the F2 generation produce different F3 individuals and thus different RI lines, such that however many different combinations of F2 individuals are bred results in that many different RI lines being established. These RI lines are homozygous at every locus.

Once the RI lines are established, they are used as is in mapping experiments. Thus, and contrary to the Patent Office's assertion, Diehl does not teach that AXB and BXA were crossed to produce heterozygotes. Since this is not how RI lines are used for mapping, applicants respectfully submit that Diehl does not teach a renewable population of genetically diverse individuals. All of the mice that are disclosed in Diehl are recombinant inbred mice, and recombinant inbred mice are known to be homozygous at every locus. The only breedings that are disclosed in this reference are breedings that are used to maintain the RI lines, which one of ordinary skill in the art would understand would be sib matings that would result in maintenance of the homozygosity of the animals of the RI lines. Therefore, applicants respectfully submit that Diehl does not teach a renewable population of genetically diverse individuals.

Therefore, applicants respectfully submit that Diehl does not support a rejection of the claims under 35 U.S.C. § 102(b) because Diehl does not generate any genetically diverse individuals, and thus cannot be read to teach mapping the genomes of genetically diverse individuals to identify genetic loci. As such, applicants respectfully submit that the rejection of claims 1-10, 15, 19-27, 46-53, 64-73, and 75 under 35 U.S.C. § 102(b) over Diehl is improper. Claim 75 has been canceled, and thus the instant rejection is believed to be moot as to this claim. Accordingly, applicants respectfully request that the instant rejection of claims 1-10, 15, 19-27, 46-53, and 64-73 be withdrawn at this time.

VI. Responses to the Obviousness Rejections

VI.A. Response to the Rejection over Diehl in view of Dindzans and Hedrich

Claims 11-14, 16-18, and 63-73 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans, and further in view of Hedrich. The asserted teachings of the Diehl reference are presented hereinabove. According to the Patent Office, the Diehl reference does not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines or that the genetically diverse individuals will be a natural by product from the use of multiple parent strains. This deficiency is asserted to be cured by Dindzans, which the Patent Office contends teaches that

multiple parents are necessary for the breeding of mice in an attempt to map genes and in the elucidation of mechanisms of genetic control. The Patent Office further asserts that Dindzans does not teach the derivation of RI lines from at least 3, 4, or 8 non-recombinant parent lines, but that Hedrich teaches the organization of breeding colonies from a founding colony made up of 8-10 breeding pairs. From this, the Patent Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the identification of a genetic locus that modulates a phenotype method Diehl so as to have included the diverse population of non-recombinant parent lines of Dindzans and to have derived their breeding population from at least 3, 4, or 8 non-recombinant parent lines as taught in further view of Hedrich for the expected benefit that more parents would obviously result in a more diverse progeny, but also from the expected benefit of providing an additional means for furthered variation among mouse lines and for the ability taught by Hedrich of making "it possible to select among the lines that one which matches the original standards best".

After careful consideration of the rejection and the Patent Office's bases therefore, applicants respectfully traverse the rejection and submit the following remarks.

Preliminarily, applicants note that the U.S. Court of Appeals for the Federal Circuit (CAFC) has set forth in *Hodosh v. Block Drug Co.*, 786 F.2d 1136 (Fed. Cir. 1986) the "tenets of patent law that must be adhered to when applying §103", *Id.* at 1143, n.5. Those tenets set out in *Hodosh* are:

- a) the claimed invention must be considered as a whole;
- b) the references must be considered as a whole and suggest the desirability and thus obviousness of making the combination;
- c) the references must be reviewed without benefit of hindsight vision afforded by the claimed invention; and
- d) "ought to be tried" is not the standard with which obviousness is determined.

All relevant evidence on each of these four dispositive issues must be fully considered and evaluated to determine whether the claimed invention would have been obvious. Additionally, it is well known that for an obviousness-type rejection to stand, the cited

document or combination must teach or suggest each element of the claimed invention; contain a suggestion to modify the cited document(s) to arrive at the claimed invention; and there must be a reasonable chance of success.

Applicants respectfully submit that Diehl in view of Dindzans, and further in view of Hedrich does not meet the requirements for a *prima facie* case of obviousness. For example, applicants respectfully submit that the combination of Diehl, Dindzans, and Hedrich does not teach or suggest each and every element of the claims, and further that this combination in fact teaches against the subject matter recited in claims 11-14, 16-18, and 64-73.

To elaborate, applicants respectfully submit that claims 11-14 recite *inter alia* a method for identifying a genetic locus that modulates a phenotype by mapping the genomes of a renewable population of genetically diverse individuals wherein one or more of the genetically diverse individuals are heterozygous for a detectable polymorphism. With regard to the teachings of Diehl, applicants respectfully submit that this reference employs individuals that are inbred, and thus are homozygous at every locus.

With regard to the Dindzans reference, applicants respectfully submit that this disclosure, like Diehl, relates to the use of recombinant inbred strains. As is known in the art, RI strains are homozygous at every locus. This is clearly pointed out in the Dindzans reference itself, which on page 2355 states that “each RI strain consists of a unique assortment of parental genes that are homozygous at every locus”, and that “such strains are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control”. Thus, Dindzans does not teach or suggest the use of heterozygous mice, and in fact, it teaches against the use of such mice. This is because the homozygosity that is a hallmark of RI lines is that which makes them “useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control”, according to Dindzans. As such, applicants respectfully submit that both Diehl and Dindzans teach against mapping the renewable populations recited in the instant claims.

Turning now to the disclosure of Hedrich, applicants respectfully submit that this reference also teaches the creation of mice that are homozygous at every locus.

Applicants respectfully submit that the citations presented by the Patent Office are from a section of Hedrich entitled "Inbred Strains". As is known in the art, inbred strains are strains that are homozygous at every locus. Thus, the entire Hedrich reference is about generating and maintaining an inbred line, and more particularly is concerned with ensuring that the line maintains its homozygosity at every locus.

This is clearly disclosed on page 170 of Hedrich, which states *inter alia* the following:

- laboratory animal populations are genetically unstable;
- strains and substrains deviate in their genotypic structure from the original genetic pattern;
- deviant alleles (foreign or new) must be detected, and if possible eliminated, in inbred strains before they are fixed in the homozygous state

Thus, Hedrich teaches techniques that can be employed for the propagation of an inbred strain and ensuring the genetic identity of its members with other members of the strain.

According to Hedrich, this is accomplished by organizing breeding colonies and testing these breeding colonies for the presence of "deviant alleles". On page 171 under the heading "**2. Organization of the Breeding Colonies**", Hedrich states that "the propagation of an inbred strain is divided into three groups: foundation colony (FC), pedigreed expansion colony (PEC), and production colony (PC)" (emphasis added). Thus, Hedrich discloses breedings designed to maintain an inbred strain.

Therefore, applicants respectfully submit that the combination of Diehl and Dindzans disclose mapping techniques that employ inbred (*i.e.*, homozygous) mice, and Hedrich teaches generally how to maintain mouse lines in a homozygous state. As such, applicants respectfully submit that the combination suggested by the Patent Office does not disclose, and in fact teaches against, the creation of individuals that are heterozygous. Thus, applicants respectfully submit that the combination of Diehl, Dindzans, and Hedrich does not support a rejection of claims 11-14, 16-18, and 64-73 under 35 U.S.C. § 103(a).

Accordingly, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of any of claims 11-14, 16-18, and 64-73.

Applicants respectfully request that the instant rejection of these claims be withdrawn at this time. Allowance of these claims is also respectfully requested.

VI.B. Response to the Rejection over Lipp in view of the '438 Patent

Claims 1-10, 15, 19-27, 46-53, and 60-75 have been rejected under 35 U.S.C. § 103(a) over the combination of Lipp and the '438 Patent. According to the Patent Office, Lipp teaches a method for identifying a genetic locus that modulates a phenotype, the method comprising:

- (a) providing a renewable population of genetically diverse individuals (each different soybean or maize plant), wherein a plurality of the genetically diverse individuals are heterozygous for detectable polymorphism;
- (b) mapping the genomes (PCR detection of 2 genetic elements) of individuals within the renewable population of genetically diverse individuals that display the phenotype; and
- (c) identifying a genetic locus (35S promoter and the NOS terminator) that modulates the phenotype (insect resistant GMOs) through the mapping step (b).

The Patent Office concedes that Lipp does not teach or suggest the method wherein the renewable population of plants is produced by backcrossing recombinant inbred lines comprising less than about 500 lines and further wherein the recombinant inbred lines are derived from at least 3, 4, and 8 different non-recombinant parent lines. The Patent Office asserts, however, that this deficiency is cured by the '438 Patent, which is asserted to teach hybrid maize seed produced by crossing plants of an inbred corn line, with plants having a different genotype, and hybrid corn plants produced by growing such hybrid maize seed and teach that more than 8 recombinant inbred corn lines can be crossed to provide new hybrid seeds.

Thus, the Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Lipp with the method of the '438 Patent since the '438 Patent teach that their genetically modified Btk expression cassette acting similarly as that discussed in Lipp Bt-176, can be transformed "in any plant and particularly corn, wheat, barley, sorghum, and rice plants and more particularly corn plants derived from a transformant or

backcrossing through further breeding experiments"(Col. 9 lines 3-6). As such, the Patent Office contends that the Btk expression cassette would also prove to be similarly detected in the method of Lipp in an attempt to decipher the corn's GMO status. Furthermore, Lipp is also asserted to teach that their method of identifying 2 genetic elements through PCR (35S promoter and NOS terminator) "seems well suited to serve as a screening method to detect the presence of GMOs" especially since "these 2 genetic elements are important for the expression of genes and are present in nearly all genetically modified plants".

After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that the Patent Office appears to misinterpret the nature of the disclosure of Lipp. Applicants respectfully submit that this reference discloses using PCR to determine whether or not a given food source contains any transgenic plants (referred to generally as "genetically modified organisms" or GMOs). The identification technique involves determining whether PCR analysis can detect the presence in soybeans or corn of two genetic elements that are not normally present in these plants: the cauliflower mosaic virus 35S promoter and the *A. tumefaciens* NOS terminator. Since these elements are not generally found in soybeans or corn, but are often present in GMOs based on their widespread use in the transgenic constructs that are used to make GMOs, the presence of a 35S promoter and/or an NOS terminator in a plant population strongly suggests that a GMO is also present (e.g., has "contaminated") the plant population. Thus, PCR is used to detect the presence of these elements in plant populations.

The instant rejection is based at least in part on the assertion that this PCR detection strategy is a mapping technique. Applicants respectfully submit that this assertion is believed to be unfounded. The Patent Office acknowledges that "mapping" is defined in the specification to refer to a method for describing a position of a genetic locus in terms of recombination frequency with a genetic polymorphism. The PCR method that the Patent Office asserts is a mapping method does not serve this purpose, however. Applicants respectfully submit that PCR detection of the presence of a promoter or of a terminator in a plant does not describe the position of the promoter or

the terminator in terms of a recombination frequency with a genetic polymorphism. In fact, applicants respectfully submit that the PCR strategies disclosed in Lipp would have generated the same data output regardless of where in the genome the 35S promoter or the NOS terminator was located. Thus, applicants respectfully submit that Lipps' PCR detection is not mapping.

Additionally, applicants respectfully submit that the Patent Office reliance on the alternative definition for "mapping" on the University of California website does not support the instant rejection. Particularly, applicants respectfully submit that the definition cited by the Patent Office states that mapping is the determination of the relative locations on genetic information on chromosomes. The PCR strategy disclosed in Lipp does not teach any relative locations on chromosomes, and in fact does not teach any locations on chromosomes at all. All the disclosed PCR strategies disclosed in Lipp are capable of doing is determining whether or not a 35S promoter or an NOS terminator are present. There is no localization to a chromosome of either of these elements in any plant, and thus there can be no identification of its position relative to anything else.

Furthermore, since no mapping step is performed, no loci are identified through the mapping step that modulate a phenotype as recited in claims 1, 46, 60, 64, 74, and 75. Thus, Lipp does not disclose or suggest at least this step of the instantly claimed methods.

Continuing with the instant rejection, applicants respectfully submit that the 35S promoter and the NOS terminator are also not properly characterized as genetic loci, and certainly do not themselves modulate any phenotype. Rather, applicants respectfully submit that the ROUNDUP READY® plants are glyphosate resistant and insect resistant, but that these phenotypes are interrelated and result from the presence of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). EPSPS is a transgene carried by ROUNDUP READY® plants, and in some embodiments the EPSPS coding sequence is frequently operably linked to a 35S promoter and an NOS terminator in an expression vector that is introduced into said plants. Therefore, applicants respectfully submit that one of ordinary skill in the art would not have sought to map the 35S promoter, the EPSPS coding sequence, or the NOS terminator in a

plant because (a) this elements are part of a transgene that would be expected to be in different locations in different transgenic plant lines; and (b) one of ordinary skill in the art would already know what genetic locus modulates the glyphosate resistance and insect resistance in these plants.

Continuing, applicants respectfully submit that the Patent Office's assertion that the presence of insects is a non-genetic factor that modulates a phenotype is believed to be unfounded. Applicants respectfully submit that ROUNDUP READY® plants are insect resistant whether or not there are any insects present. Applicants respectfully submit that the instant specification defines "modulate" in the context of a phenotype, to refer to:

the action of a genetic or non-genetic factor to contribute to the phenotype. Modulation can promote or detract from expressivity or penetrance of the phenotype. Alternatively or in addition, modulation can add or subtract specific features of a phenotype. A modulatory contribution can be dramatic or subtle, the only requirement being that it is ultimately detectable.

Specification at page 17, lines 15-20 (emphasis added). The presence or absence of insects does not contribute whether the plant is insect resistant, does not promote or detract whether the plant is insect resistant, and does not add or subtract any features from the plant being insect resistant. At best, applicants respectfully submit that the presence of insects might provide the material by which the insect resistance phenotype can be assayed, but the insects themselves do not impact in any way whether the disclosed plants are in fact insect resistant. Thus, applicants respectfully submit that the presence of insects cannot be interpreted to modulate a phenotype.

Summarily, applicants respectfully submit that the Patent Office's characterization of Lipp is believed to be inaccurate. Lipp does not disclose any genetically diverse individuals, does not disclose mapping the genomes of any genetically diverse individuals, and thus does not disclose identifying any genetic loci that modulate any phenotype through the mapping step. Thus, applicants respectfully submit that Lipp does not support a rejection of claims 1-10, 15, 19-27, 46-53, and 60-75 under 35 U.S.C. § 103(a).

Turning now to the disclosure of the '438 Patent, applicants respectfully submit that the '438 Patent does not cure the deficiencies set forth hereinabove with respect to Lipp. Applicants respectfully submit that the '438 Patent discloses inbred corn lines containing novel expression constructs. These novel constructs are designed to encode toxins that confer insect resistance to the inbred corn plants that contain the constructs. The '438 Patent also discloses hybrid seed that can be generated by crossing inbred corn plants.

However, applicants respectfully submit that contrary to the Patent Office's assertion, the '438 Patent does not teach recombinant inbred lines that are derived from at least 3, 4, or 8 different non-recombinant parent lines. Rather, applicants respectfully submit that column 4, lines 44-48, of the '438 Patent merely discloses cross-pollinating one inbred line with another (*i.e.*, one other) inbred line. Therefore, at best the '438 Patent might be understood to disclose a series of F1 hybrid seeds derived from pairwise breedings among the 15 disclosed lines, but does not disclose or suggest making any hybrids that include genetic contributions from more than two such inbred lines.

Applicants respectfully submit that in both Lipp and the '438 Patent, the genetic locus that causes the insecticidal phenotype is known. In the former, it is the EPSPS coding sequence, and in the latter it is the Bt toxin coding sequence. Since the loci are known in both Lipp and the '438 Patent, there would have been no motivation to map them. Thus, one of ordinary skill in the art would not have been motivated to identify these loci through mapping as recited in the instant claims. Absent this motivation to combine the references as suggested by the Patent Office, applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Accordingly, applicants respectfully submit that the combination of Lipp and the '438 Patent does not support a rejection of claims 1-10, 15, 19-27, 46-53, and 60-75 under 35 U.S.C. § 103(a). Claim 75 has been canceled, and thus the instant rejection is believed to be moot as to this claim. As such, applicants respectfully request that the instant rejection of claims 1-10, 15, 19-27, 46-53, and 60-74 be withdrawn, and that the claims be allowed at this time.

VII. Discussion of the New Claims

New claims 76 and 77 have been added. Support for the new claims can be found throughout the specification as filed, including particularly at page 6, lines 18-20. Accordingly, no new matter has been added as a result of the addition of the new claims.

Applicants respectfully submit that claims 76 and 77 are believed to be distinguished from the cited references based on their dependence from distinguished claim 46 and 74, respectively. Accordingly, applicants respectfully submit that claims 76 and 77 are in condition for allowance at this time.

CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

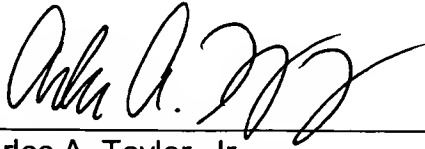
DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: March 21, 2007

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